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EXAMINER	
GRUN, JAMES LESLIE	
ART UNIT	**PAPER NUMBER**
1641	

NOTIFICATION DATE	DELIVERY MODE
10/18/2007	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/784,163	TACHA, DAVID	
	Examiner	Art Unit	
	James L. Grun	1641	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 August 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *81,85,87,91 and 104-115* is/are pending in the application.

4a) Of the above claim(s) *111-115* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *81,85,87,91 and 104-110* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *81,85,87,91 and 104-115* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

The amendment filed 10 August 2007 is acknowledged and has been entered. Claims 104-115 are newly added. Claims 1-80, 82-84, 86, 88-90, and 92-103 have been cancelled. Claims 81, 85, 87, 91, and 104-115 remain in the case.

Newly submitted claims 111-115 are directed to an invention that is independent or distinct from the invention originally claimed for the following reasons: the inventions as now claimed in claims 111-115 and that as originally claimed in claims 81, 85, 87, and 91, and now also 104-110, are related as combination and subcombination. Inventions in this relationship are distinct if it can be shown that (1) the combination as claimed does not require the particulars of the subcombination as claimed for patentability, and (2) that the subcombination has utility by itself or in other combinations (MPEP § 806.05(c)). In the instant case, the combination as claimed does not require the particulars of the subcombination as claimed because the method has been found separately patentable in US 6,580,056 without requirement for detection of two or three or more antigens. The subcombination has separate utility such as with the use of other than a pressure cooker for heat-mediated antigen retrieval or with the use of other than heat for antigen retrieval or with the use of samples, such as cryostat sections, that do not require antigen retrieval.

Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claims 111-115 are withdrawn from consideration as being directed to a non-elected invention. See 37 CFR § 1.142(b) and MPEP § 821.03.

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The specification is objected to under 35 U.S.C. § 112, first paragraph, as failing to provide an adequate written description of the invention, and failing to adequately teach how to make and/or use the invention, i.e. failing to provide an enabling disclosure.

Claims 81, 85, 87, 91, and 104-110 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. With regard to these claims, the specification, as originally filed, does not provide support for the invention as is now claimed.

Applicant teaches that detection of more than two antigens requires sequential treatments (see e.g.: pages 16-17; original claims 72, 74, 83, 85, 89, or 91) and provides no guidance for simultaneous triple, or more, staining with three, or more, different simultaneous primary and three, or more, different simultaneous secondary antibodies as is now claimed. Although one of skill in the art might realize from reading the disclosure that simultaneous detection of three antigens with three simultaneous primary and three simultaneous secondary antibodies is useable in the invention, such possibility of use does not provide explicit or implicit indication to one of skill in the art that such a format was originally contemplated as part of applicant's invention and such possibility of use does not satisfy the written description requirements of 35 U.S.C. § 112, first paragraph.

Applicant teaches buffers with various pH ranges, in particular a Tris-HCl buffer in a pH range of about 5.7 to about 6.5 is taught. Although one of skill in the art might realize from reading the disclosure that other buffers with other pH ranges are useable, and perhaps preferable, in the invention, such possibility of use does not provide explicit or implicit indication to one of skill in the art that the pH ranges as are now claimed, and in particular a Tris-HCl buffer having the pH range as is now claimed, were originally contemplated as part of applicant's invention and such possibility of use does not satisfy the written description requirements of 35 U.S.C. § 112, first paragraph.

Applicant teaches pairs of antigens suitable for detection together (see e.g. original claim 71) and provides no written description for many of the antigen pairs or groups as are now claimed. Although one of skill in the art might realize from reading the disclosure that other antigen combinations are useable in the invention, such possibility of use does not provide explicit or implicit indication to one of skill in the art that specific combinations as are now claimed were originally contemplated as part of applicant's invention and such possibility of use does not satisfy the written description requirements of 35 U.S.C. § 112, first paragraph.

Note that a description which renders obvious a claimed invention is not sufficient to satisfy the written description requirement. Applicant is requested to direct the Examiner's attention to specific passages where support for these newly recited limitations can be found in the specification as filed or is required to delete the new matter.

Moreover, these claims are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the

invention. Applicant does not disclose other than the simultaneous use of two secondary antibodies labeled with horseradish peroxidase and alkaline phosphatase. Absent further written description and guidance from applicant, one would not readily envision how to accomplish simultaneous labeling with different secondary antibodies for the number of primary antibodies and antigens encompassed by these claims. The art would suggest that more than three simultaneous stainings would be difficult to discriminate (see e.g. van der Loos (1999), page 64). Moreover, the art would suggest that Tris is a poor buffer below pH 7.5 (see USB Tech Library) and it is not clear how one would use a buffering agent at a pH outside of its effective range as suitable for stabilizing any composition. A patent is granted for a completed invention, not the general suggestion of an idea and how that idea might be developed into the claimed invention. In the decision of *Genentech Inc. v. Novo Nordisk*, 42 USPQ 2d 1001 (CAFC 1997), the court held that: "[p]atent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable" and that "[t]ossing out the mere germ of an idea does not constitute enabling disclosure." The court further stated that: "when there is no disclosure of any specific starting material or of any of the conditions under which a process is to be carried out, undue experimentation is required; there is a failure to meet the enablement requirements that cannot be rectified by asserting that all the disclosure related to the process is within the skill of the art", "[i]t is the specification, not the knowledge of one skilled in the art, that must supply the novel aspects of an invention in order to constitute adequate enablement."

Applicant's arguments filed 10 August 2007 have been fully considered but they are not deemed to be persuasive.

Notwithstanding applicant's assertions to the contrary, applicant's amendments are not free of new matter for at least the reasons set forth above.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 81, 85, 87, 91, and 104-110 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In claim 81 and claims dependent thereupon, "the at least three . . . complexes" lack antecedent basis. It is not clear what applicant intends as encompassed within the metes and bounds of the method because it is not clear which three antigen-antibody complexes are sufficient for the detecting step, e.g. the detection of a complex of the first secondary antibody bound to the first primary antibody bound to antigen in sample meets detection of two of the complexes as claimed because the first primary antibody is antigen for the first secondary antibody. The claims are confusing because, for the reasons set forth immediately above, the preamble recites detecting three or more antigens in sample but the body of the claims do not recite a step relating detecting formation of at least three antigen-antibody complexes to detecting three or more antigens in sample.

In claim 85 and claims dependent thereupon, "the formation" lacks antecedent basis.

In claim 87 and claims dependent thereupon, "the at least three . . . complexes" lack antecedent basis. It is not clear what applicant intends as encompassed within the metes and bounds of the method because it is not clear which three antigen-antibody complexes are

sufficient for the detecting step, e.g. the detection of a complex of the first secondary antibody bound to the first primary antibody bound to antigen in sample meets detection of two of the complexes as claimed because the first primary antibody is antigen for the first secondary antibody. The claims are confusing because, for the reasons set forth immediately above, the preamble recites detecting three or more antigens in sample but the body of the claims do not recite a step relating detecting formation of at least three antigen-antibody complexes to detecting three or more antigens in sample.

In claim 91 and claims dependent thereupon, "the formation" lacks antecedent basis.

Claims 104-106 are improper because they fail to end in a period. Moreover, improper Markush language is used to claim the members of the groups. The alternatives "selected from...or" or "selected from the group consisting of...and" are acceptable. In these claims, acronyms should be defined.

In claims 104 and 105: a period is found after "light chain" thus it is not clear if applicant intended the pairs following this as encompassed; the recitations of "+" should be --and--; and, the recitation of "Ki-67 and ER; or ER + K-67" appears redundant because it is believed --Ki-67-- was intended and the order of the members of the pairs does not appear of any relevance.

In claim 106, the meaning of "Synaptophysin (6)" is not clear.

In claim 107, "the . . . cocktails" lack antecedent basis. It is not clear what is intended by "at least a 5 or 6 primary antibodies."

In claim 108, "the . . . cocktails" lack antecedent basis. It is not clear what is intended by "at least a 5 or 6 primary antibodies."

In claims 109 and 110, "comprises is" is not clear. In these claims, acronyms should be defined.

Applicant's arguments filed 10 August 2007 have been fully considered but they are not deemed to be persuasive.

Notwithstanding applicant's assertions to the contrary, applicant's amendments have not obviated rejections under this statute for the reasons set forth above.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 103 which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.
> (c) Subject matter developed by another person, which qualifies as prior art only under one or more subsections (e), (f) and (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

Claims 81, 85, 87, 91, and 104-108 are rejected under 35 U.S.C. § 103 (a) as being unpatentable over C. M. van der Loos (1999) in view of applicant's admissions and either of Myers et al. (J. Surg. Pathol. 1: 105, 1995) or Hasui et al. (J. Histochem. Cytochem. 51: 1169, 2003) for reasons similar to those of record in the prior rejection of the similar subject matter of prior claims 81-103. In addition to the teachings of the reference set forth in the prior Office action, the handbook of C. M. van der Loos teaches that indirect/indirect/indirect simultaneous triple staining using cocktails of primary antibodies from different animal species and/or of different immunoglobulin isotypes and/or of different immunoglobulin classes and cocktails of labeled secondary antibodies specific for the primary antibodies (see pages 28, 29, 63-65, and

110-112), as well as other variations such as indirect/indirect/direct simultaneous triple staining, were well known to the art. In addition, the conventional use of Tris or phosphate buffers is taught (see e.g. page 77).

Applicant's arguments filed 10 August 2007 have been fully considered but they are not deemed to be persuasive.

Notwithstanding applicant's assertions to the contrary, for the reasons of record and as set forth above the reference of C. M. van der Loos clearly teaches immunoenzyme multiple staining protocols, including an exemplification of simultaneous triple staining (see in particular Plate 13 and the methodology therefor on pages 28-29 and 110) and reference to other publications performing similar protocols (see pages 63-65), and the direction to combine protocols sequentially to achieve staining of more antigens.

Claims 109 and 110 are rejected under 35 U.S.C. § 103(a) as being unpatentable over C. M. van der Loos (1999) in view of applicant's admissions and either of Myers et al. or Hasui et al., as applied to claims 81, 85, 87, 91, and 104-108 above, and further in view of Chien et al. (US 6,537,745) and any or all of Loor et al. (US 4,690,890), Philo et al. (US 5,108,896), Diamandis et al. (US 5,089,423), and Damaj et al. (US 2002/0173053).

The teachings of the combination of C. M. van der Loos (1999), applicant's admissions, Myers et al. and/or Hasui et al. are as set forth in the previous Office action and above. In contrast to the invention as instantly claimed the references do not teach additional components in a buffer such as bovine serum albumin or sodium azide.

Chien et al. teach that substitution of reagents in a buffer with reagents performing essentially the same function is well known in the art, such as substitution of borate with phosphate buffering agents, or substitution of gelatin with albumin or other blocking agents (cols. 3, 6-7, 9), or substitution of a single blocking agent with a mixture thereof (see cols. 6-7).

Loor et al. teach immunoassays, for the detection of multiple antigens, which may use different enzyme labels on antigen-specific antibodies in a mixture to detect the different antigens (col. 6-8). The reference teaches that immunoassays are typically performed at pH 6-9 (col. 8). The reference teaches antibody diluents having 0.05M Tris, 0.05% preservative, 1.0% bovine serum albumin (BSA), and 100 mM NaCl (col. 15), or 0.05M Tris, 0.05% preservative, 5.0% BSA, and 100 mM NaCl (col. 16).

Philo et al. teach immunoassays, for the detection of multiple antigens, which may use different labels on antigen-specific antibodies in a mixture to simultaneously detect the different antigens. The antibody mixtures were diluted in a buffer comprising 0.1M Tris/HCl, 0.2% sodium azide, 0.5% BSA, serum, and 100 mM NaCl (col. 11).

Diamandis et al. teach antibody diluents of various formulations, e.g.: 0.01M Tris, 0.01% sodium azide, 1% BSA, and 0.01% thimerosal (col. 11); 0.05M Tris, 0.05% sodium azide, 0.5% BSA, 0.01% TWEEN, 150 mM NaCl (col. 14); or, 0.05M Tris, 0.05% sodium azide, 1.0% BSA, 150 mM NaCl (col. 20).

Damaj et al. teach simultaneous antigen detection by immunohistochemistry. Mixtures of different antibody populations, specific for different markers to be determined, each conjugated to a different enzyme, e.g. horseradish peroxidase and alkaline phosphatase (see [0027], [0036], [0046] and claim 7), were made in blocking buffer (see [0027]). Blocking buffer

comprised borate buffer, 0.05% TWEEN 20, 0.25% bovine serum albumin, and 0.05% sodium azide. Substrates for the different enzymes were added sequentially ([0047]). The reference teaches alternative labeling known to the art ([0006]). The reagents are provided in a kit ([0013]).

It would have been obvious to one of ordinary skill in the art at the time the instant invention was made to have used buffers including preservatives and carrier/blocker proteins in the compositions and methods of van der Loos, as modified, in order to achieve a desired pH in the range of 6-9, preserve the composition, and prevent non-specific loss of the active composition components because to do so is conventional in the immunoassay art as taught in any or all of Loor et al., Philo et al. (US 5,108,896), Diamandis et al. (US 5,089,423), and Damaj et al. (US 2002/0173053). One would have been motivated to have adjusted the buffer components within the ranges known to the art, such as in the compositions taught in any of the references, with an expectation that the components would perform their desired functions, such as buffering, blocking, or preserving, in the antibody diluent/blocking compositions. It would have also been obvious to one of ordinary skill in the art at the time the instant invention was made to have substituted reagents in the antibody buffer compositions for use in the methods of van der Loos, as modified, with those performing essentially the same function because to do so is routine in the art as taught in Chien et al.

Thus, the claimed invention as a whole was clearly prima facie obvious, especially in the absence of evidence to the contrary.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR § 1.136(a).

A SHORTENED STATUTORY PERIOD FOR REPLY TO THIS FINAL ACTION IS SET TO EXPIRE **THREE MONTHS** FROM THE MAILING DATE OF THIS ACTION. IN THE EVENT A FIRST REPLY IS FILED WITHIN **TWO MONTHS** OF THE MAILING DATE OF THIS FINAL ACTION AND THE ADVISORY ACTION IS NOT MAILED UNTIL AFTER THE END OF THE **THREE-MONTH** SHORTENED STATUTORY PERIOD, THEN THE SHORTENED STATUTORY PERIOD WILL EXPIRE ON THE DATE THE ADVISORY ACTION IS MAILED, AND ANY EXTENSION FEE PURSUANT TO 37 C.F.R. § 1.136(a) WILL BE CALCULATED FROM THE MAILING DATE OF THE ADVISORY ACTION. IN NO EVENT WILL THE STATUTORY PERIOD FOR REPLY EXPIRE LATER THAN **SIX MONTHS** FROM THE MAILING DATE OF THIS FINAL ACTION.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to James L. Grun, Ph.D., whose telephone number is (571) 272-0821. The examiner can normally be reached on weekdays from 9 a.m. to 5 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Long Le, SPE, can be contacted at (571) 272-0823.

The phone number for official facsimile transmitted communications to TC 1600, Group 1640, is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application, or requests to supply missing elements from Office communications, should be directed to the Group receptionist whose telephone number is (571) 272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/JLG/
James L. Grun, Ph.D.
October 12, 2007

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